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How Frequently Is Venous Thromboembolism in Heparin-Treated Patients Associated With Heparin-Induced Thrombocytopenia?

Robert L. Levine, MD, FCCP; David McCollum, MS; and Marcie J. Hursting, PhD

Background: Patients receiving heparin for thromboprophylaxis or treatment may have new or recurrent venous thromboembolism (VTE) if immune-mediated heparin-induced thrombocytopenia (HIT) occurs or for other reasons, eg, if anticoagulation fails. We estimated from the literature how frequently a patient presenting with VTE during or following heparin therapy has HIT-associated VTE.

Methods: A comprehensive, systematic literature search was conducted to identify studies using unfractionated or low-molecular-weight heparin (LMWH) for thromboprophylaxis or treatment in which new or recurrent VTE and serologically confirmed HIT were reported. From extracted study data, the proportion of patients with HIT-associated VTE relative to any VTE was calculated by heparin type and mode of administration.

Results: We identified 10 studies, some with multiple arms, that used unfractionated heparin (IV administration, 5 studies; subcutaneous administration, 3 studies) or subcutaneous LMWH (5 studies) and met analysis criteria. Across these studies, 386 of 6,219 heparin-treated patients had VTE, including 32 patients who also had HIT. The frequency of HIT-associated VTE among heparin-treated patients with VTE was comparable between IV and subcutaneous unfractionated heparin therapy (13.2% [17 of 129 patients] vs 12.4% [14 of 113 patients]; odds ratio, 1.07; 95% confidence interval, 0.50 to 2.3; $p > 0.99$) yet significantly different between unfractionated heparin and LMWH therapy (12.8% [31 of 242 patients] vs 0.7% [1 of 144 patients]; odds ratio, 21.0; 95% confidence interval, 2.8 to 156; $p < 0.001$).

Conclusions: VTE is associated with HIT infrequently (< 1%) in LMWH-treated patients, yet often (approximately one in eight cases) in unfractionated heparin-treated patients. Physicians should suspect the possibility of HIT if VTE develops during or soon after unfractionated heparin use; if thrombocytopenia is present, alternative anticoagulation should be used until HIT is excluded. (CHEST 2006; 130:681–687)

Key words: adverse effects; anticoagulant drugs; heparin; thrombocytopenia; thrombosis; venous thrombosis

Abbreviations: HIT = heparin-induced thrombocytopenia; LMWH = low-molecular-weight heparin; VTE = venous thromboembolism

Unfractionated heparin and low-molecular-weight heparins (LMWHs) are routinely used for thromboprophylaxis or treatment.¹ Despite heparin therapy, patients sometimes have new or recurrent thrombosis if anticoagulation fails or heparin-induced thrombocytopenia (HIT) occurs. HIT is a serious, immune-mediated condition in which 38 to 76% of patients acquire thrombotic complications, typically venous thromboembolism (VTE), in the

days to weeks after its onset.² In patients with HIT or the reactive antibodies that cause HIT, continued exposure or re-exposure to heparins can result in catastrophic outcomes.³ Treatment strategies for VTE differ: if VTE is not associated with HIT, heparins are recommended¹; if VTE is associated with HIT, heparins are contraindicated and alternative anticoagulation is recommended.⁴

Although VTE as a complication of HIT is well

described,⁴⁻⁸ the recognition of HIT (or HIT-associated thrombosis) can be challenging. Patients with HIT often have relative rather than absolute thrombocytopenia (a decrease of 50% in the platelet count yet a nadir $> 150 \times 10^9/L$). Platelet counts in HIT typically normalize within days of discontinuing heparin even though the thrombotic risk persists for weeks. It is possible for heparin-treated patients to be discharged from the hospital before their HIT manifests and then return with HIT-associated

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thrombosis.^{5,6} Physicians are encouraged to be vigilant in suspecting HIT in anyone presenting with thrombosis following recent (or current) heparin therapy or recent hospitalization; however, the likelihood that a new or recurrent VTE in a heparin-treated patient is associated with HIT remains unclear. Its clarification is important for facilitating HIT risk assessment and treatment decision making in the heparin-treated patient presenting with VTE.

We conducted a systematic literature analysis to address the question, "how frequently is new or recurrent VTE in a heparin-treated patient associated with HIT?" Because unfractionated heparin is more likely than LMWH to cause HIT,⁴ we considered the question separately for these heparin types.

MATERIALS AND METHODS

Literature Search

Articles were to be included in this analysis if they met the following criteria: the study design was a randomized control trial or a prospective or retrospective cohort study that evaluated consecutive patients (or data reanalysis of such studies); unfractionated heparin or LMWH was administered for prophylaxis or treatment of thrombosis; the definition of HIT was clearly stated, with confirmatory laboratory testing for HIT conducted; objectively documented new or recurrent VTE, including deep venous

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thrombosis, pulmonary embolism, or both, were reported for patients with HIT as well as all patients; and at least one VTE occurred in the relevant study arm(s).

To identify potentially relevant articles, a search was performed using the Medline database (November 1984 to November 2004) and the Cochrane Library (*The Cochrane Library* 2004, issue 4) and the search terms "heparin-induced thrombocytopenia" or "heparin-associated thrombocytopenia" together with "thrombosis" or "thromboembolism." A search was also performed using the Medline database (November 1984 to November 2004) and the terms "heparin" and "thrombosis" and "thrombocytopenia." The searches were limited to English-language publications and human studies, and for the latter search, randomized clinical trials. A total of 673 unique citations were identified. The titles and abstracts of the citations, when available, were reviewed and coded as "irrelevant" or "possibly relevant" to our research question and associated criteria. Articles that were considered possibly relevant ($n = 41$) were retrieved in full for in-depth review. Additional search strategies used to find potentially relevant articles included scanning the text and bibliographies of summary articles, books, and other publications related to VTE or HIT and reviewing personal files. Possibly relevant articles were screened with respect to our inclusion criteria by one investigator and included in the analysis on independent review and consensus agreement of its eligibility by another investigator.

Data Analysis

From eligible articles, the numbers of patients who received heparin, who acquired VTE, and who acquired HIT and VTE were extracted and tabulated. We defined HIT-associated VTE as an event that occurred in a patient with HIT. For VTE occurring in a patient lacking HIT, the event was considered "not associated with HIT" and no further attribution of cause was attempted. The proportion of patients with HIT-associated VTE compared with patients with any VTE (and the exact 95% confidence interval) was calculated for each study and across the studies according to the type of heparin administered (unfractionated or low-molecular-weight), accounting for its method of administration (IV or subcutaneous). For the across-study values, the odds ratio (and associated 95% confidence interval) was determined for IV vs subcutaneous unfractionated heparin therapy and for unfractionated vs LMWH therapy; a Fisher Exact Test was used for assessing significance. In heparin-treated patients with VTE, the frequency of HIT was compared between surgical and medical patients using a Fisher Exact Test. Statistical analyses were conducted using statistical software (GraphPad Statistical Software; GraphPad Software; San Diego, CA), and significance was declared at $p < 0.05$.

RESULTS

Data Set

From 41 possibly relevant articles identified from the literature database search, we found 9 articles involving eight clinical studies that met inclusion criteria for our analysis.⁹⁻¹⁷ The remaining 32 articles failed to meet one or more inclusion criteria, most often ($n = 23$) lacking reported outcomes for patients with HIT and/or a prospective definition of HIT or confirmatory testing. The nine eligible articles included both an analysis¹⁷ and reanalysis¹² of

HIT occurring in a single clinical study.¹⁸ In the initial analysis, HIT was defined as a platelet count $< 150 \times 10^9/L$ and in the reanalysis as a $\geq 50\%$ fall in the platelet count from the postoperative peak. The investigators considered the latter definition to be improved because it provided greater sensitivity and similar high specificity for detecting HIT. Hence we extracted data from the reanalysis¹² and, where needed, the original study report¹⁸; and the initial analysis¹⁷ is not presented separately herein. From our supplemental search strategies, which included scanning bibliographies of related articles and reviews, we identified 2 more articles that also met our criteria,^{19,20} yielding a total of 10 studies for our analysis.

Table 1 summarizes the purpose, design, patient population, heparin dosing information, and follow-up period of each of the 10 studies. There were six randomized controlled trials,^{9–12,19,20} three prospective studies,^{13–15} and one retrospective study.¹⁶ The studies may have had multiple study arms. The comparator in two studies^{19,20} was the selective factor Xa inhibitor fondaparinux, and no VTE occurred in the subcutaneous unfractionated heparin arm of another study¹¹; these study arms were not included in our analyses. One study¹⁶ was conducted in pediatric patients, and the other studies were in adults. In each study, medical or surgical patients received IV unfractionated heparin (five studies), subcutaneous unfractionated heparin (three studies), or subcutaneous LMWH (five studies) therapy typically for 7 to 10 days. Patients were followed up in the hospital or after discharge at most for 90 days for new or recurrent VTE. Two studies^{9,12} were of orthopedic surgical patients, who are at increased risk of HIT compared with cardiac surgery patients.⁴ Across the studies, four different LMWHs were used: dalteparin,¹¹ enoxaparin,¹⁹ fraxiparin,⁹ and reviparin.¹⁰ In each of three studies^{15–17} reporting the animal source of the unfractionated heparin, porcine-derived heparin was used. In each of four studies^{10,13,19,20} of heparin therapy for acute VTE, patients also received longer-term anticoagulation with a vitamin K antagonist typically for up to 90 days. In one study,⁹ antithrombotic treatment after the 9- to 11-day study period was at the discretion of the investigator, and 88% of patients also received continued therapy for an average of 4 to 6 weeks using unfractionated heparin, LMWH, vitamin K antagonist, aspirin, or a combination of these.

HIT was prospectively defined in the studies, typically as a platelet count $< 100 \times 10^9/L$ or a 40 to 50% decrease in count, with serologic confirmation (Table 2). Thrombocytopenia without laboratory confirmation of heparin-dependent antibody was not considered HIT in our analyses. By single exception,

confirmatory laboratory testing was not performed in 2 of 11 unfractionated heparin-treated patients with VTE and HIT in one study.¹² Their HIT was diagnosed based on the platelet count criteria being met, other causes of thrombocytopenia being excluded, and the platelet count recovering on heparin cessation.

Frequency Estimates

For each study and overall, we estimated the frequency of VTE, HIT-associated VTE, and their relative proportion, by type of heparin (Table 3). In one study,¹⁶ only 38 of 57 patients with thrombosis had plasma available for heparin-dependent antibody testing, and we based frequency estimations on the tested patients only. It is possible that some events among the tested patients were arterial rather than venous, and hence the relative proportion of HIT-associated venous events to any “venous” event may be underestimated for this study. Although not reported in Table 3, an additional five patients in the unfractionated heparin arm of one study⁹ had VTE within 30 to 50 days after the 9- to 11-day study period; it was unclear if they had HIT. In general, frequency estimates of VTE and HIT-associated VTE were fairly comparable across studies of unfractionated heparin and those of LMWH.

Overall, of 6,219 patients administered unfractionated heparin ($n = 3,792$) or LMWH ($n = 2,427$), VTE occurred in 386 patients, 32 of whom had HIT. Of 386 patients with VTE, there were 348 adults, of whom 154 were postoperative orthopedic or craniotomy patients; and 38 pediatric patients, of whom the number of surgical patients could not be determined from available data. In the adults with VTE, 14 of 154 surgical patients (9.1%) and 6 of 194 medical patients (3.1%) had HIT ($p = 0.02$). Of 12 pediatric patients with VTE and HIT, 10 patients (83.3%) had recent cardiac or abdominal surgery.

Among unfractionated heparin-treated patients with VTE, 17 of 129 IV-treated patients (13.2%) and 14 of 113 subcutaneously treated patients (12.4%) had HIT-associated VTE (odds ratio, 1.07; 95% confidence interval, 0.50 to 2.3; $p > 0.99$). Among patients with VTE from any cause, the frequency of HIT-associated VTE was 12.8% (31 of 242 patients) with unfractionated heparin therapy and 0.7% (1 of 144 patients) with LMWH therapy (odds ratio, 21.0; 95% confidence interval, 2.8 to 156; $p < 0.001$).

DISCUSSION

Each year, an estimated 2 million Americans acquire deep venous thrombosis and 600,000 acquire pulmonary embolism.²¹ Many of these patients will

Table 1—Studies in Analysis Data Set*

Study (Year)	Purpose†	Design	Population	Heparin	Dosing (Mean Duration, d)	Follow-up, d
Buller et al ¹⁹ (2004)	3	Randomized control trial	Acute DVT	LMWH sc (enoxaparin)	1 mg/kg bid (7.1)	90
Buller et al ²⁰ (2003)	3	Randomized control trial	Acute PE	UFH IV	> 5,000 IU bolus, then > 1,250 IU/h (6.9)	90
Gallus et al ¹³ (1987)	5	Prospective cohort study	Acute VTE	UFH IV	2,500 to 5,000 IU bolus, 1,125 to 1,250 IU/h (8.8)	30
Girolami et al ¹⁴ (2003)	4	Prospective cohort study	Medical	UFH sc	Prophylaxis: 10,000 to 20,000 IU/d (14); treatment: doses to achieve aPTTs of 1.5 to 3.0 times control (10)	In hospital (or heparin cessation)
Kappers-Klunne et al ¹⁵ (1997)	4	Prospective cohort study	Cardiology and neurology	UFH IV	> 833 U/h (8.3)	In hospital (or 15 d)
Leyvraz et al ⁹ (1991)	1	Randomized control trial	Orthopedic surgery	UFH sc	4,000 IU 16 h preoperatively; starting 12 h postoperatively, injections tid until postoperative days 9 to 11 to yield aPTTs of 2 to 5 s above control (mean dose 3,679 IU per injection)	9–11
				LMWH sc (fraxiparine)	41 IU/kg/d until third postoperative day (first dose 12 h preoperatively); 62 IU/kg/d on postoperative day 4 to days 9 to 11	9–11
Lindhoff-Last et al ¹⁰ (2002)	2,4	Randomized control trial	Acute DVT	UFH IV	5,000 IU bolus, 1,250 IU/h (6.3)	90
				LMWH sc (reviparin)	3,500 aXa IU bid if 35 to 45 kg, 4,200 aXa IU bid if 45 to 60 kg, or 6,300 aXa IU bid if > 60 kg (6.8)	
				LMWH sc (reviparin)	7,000 aXa IU/d if 35 to 45 kg, 8,400 aXa IU/d if 45 to 60 kg, or 12,600 aXa IU/d if > 60 kg (25)	
Macdonald et al ¹¹ (2003)	1	Randomized control trial	Craniotomy	LMWH sc (dalteparin)	2,500 IU/d starting at induction of anesthesia and continuing for 7 d or until the patient was ambulating (5.5)	30
Schmugge et al ¹⁶ (2002)	4	Retrospective cohort study	Pediatric intensive care	UFH IV	Administered for > 5 d; doses not reported	In hospital
Warkentin et al ¹² (2003)	1,4	Randomized control trial (reanalysis)	Orthopedic surgery	UFH sc	7,500 U bid beginning on first postoperative day (10)	In hospital (or 14 d)
				LMWH sc (enoxaparin)	30 mg bid beginning on first postoperative day (10)	In hospital (or 14 d)

*sc = subcutaneous; UFH = unfractionated heparin; DVT = deep venous thrombosis; PE = pulmonary embolism; aPPT = activated partial thromboplastin time; aXa = factor Xa.

†1 = Unfractionated heparin vs LMWH (compression devices in Macdonald et al¹¹) for VTE prophylaxis; 2 = unfractionated heparin vs LMWH for VTE treatment; 3 = unfractionated heparin or LMWH vs fondaparinux for VTE treatment; 4 = analysis of HIT incidence, with VTE reported; 5 = analysis of risk factors for VTE, with HIT reported.

receive heparin, which is routinely initiated (often in the emergency department) for treatment of VTE, yet is potentially catastrophic if the patient has HIT-associated VTE and/or reactive heparin-depen-

dent antibodies. HIT should be suspected whenever thrombocytopenia and/or thrombosis such as VTE occur during or soon after heparin treatment, with other causes of thrombocytopenia excluded.²² Be-

Table 2—Identification of HIT in Heparin-Treated Patients*

Study (Year)	HIT	Laboratory Confirmation
Buller et al ¹⁹ (2004)	Platelet count < 100 × 10 ⁹ /L or decreased > 40% from baseline (confirmed on retesting)	Antiplatelet antibodies†
Buller et al ²⁰ (2003)	Platelet count < 100 × 10 ⁹ /L or decreased > 40% from baseline (confirmed on retesting)	Antiplatelet antibodies†
Gallus et al ¹³ (1987)	Platelet count < 100 × 10 ⁹ /L, excluding other causes	Heparin-induced platelet aggregation
Girolami et al ¹⁴ (2003)	Platelet count decrease > 50% from baseline (confirmed by retesting) and laboratory confirmation; or combination of absence of other cause of thrombocytopenia, thrombocytopenia occurring at least 5 d after heparin start, and either normalization of platelet count by 10 d after stopping heparin or death due to unexpected thrombosis	Heparin-induced platelet activation and heparin-platelet factor 4 ELISA
Kappers-Klunne et al ¹⁵ (1997)	Platelet count > 120 × 10 ⁹ /L before heparin therapy, with decrease to < 60 × 10 ⁹ /L within 5 d or to < 100 × 10 ⁹ /L if > 50% fall from baseline, or > 30% decrease with acute thrombosis, with other causes of thrombocytopenia excluded, and a positive assay and resolution of thrombocytopenia after heparin cessation	Heparin-induced platelet activation and heparin-platelet factor 4 ELISA
Leyvraz et al ⁹ (1991)	Platelet count decreased > 40% and absolute count < 100 × 10 ⁹ /L on two consecutive measurements	Platelet aggregation test
Lindhoff-Last et al ¹⁰ (2002)	Platelet count decreased > 50% from baseline or < 100 × 10 ⁹ /L on two consecutive measurements after 5 d of therapy and increase within 8 d of heparin cessation, with other causes excluded	Heparin-platelet factor 4 ELISA
Macdonald et al ¹¹ (2003)	Platelet count decreased to < 150 × 10 ⁹ /L or by > 50% from baseline	Heparin-induced antiplatelet antibodies
Schmugge et al ¹⁶ (2002)	Platelet count decreased to < 150 × 10 ⁹ /L or by > 50% from baseline, occurring after at least 5 d of heparin, with other causes excluded	Heparin-platelet factor 4
Warkentin et al ¹² (2003)	Platelet count decreased > 50% from postoperative peak	Serotonin release assay and antiplatelet antibodies (ELISA)

*ELISA = enzyme-linked immunoassay.

†Terminology from article; associated citation in the article suggests testing was for heparin-dependent IgG antibodies.

cause heparin-treated patients may also acquire VTE due to other causes, *ie*, inadequate anticoagulation, we wondered how big the “HIT problem” is in this setting. That is, what is the risk that a patient presenting with VTE during or following heparin therapy has HIT? This question is distinct from questions related to the risk of HIT with heparin therapy, which is well documented to be < 0.1 to 5% depending on the patient population and type of heparin,^{4,23} or the risk of thrombosis in patients with HIT, which is well documented to be 38 to 76% in the absence of alternative anticoagulation.² To address our question, we conducted a literature analysis with the aim of estimating how frequently VTE in heparin-treated patients is associated with HIT.

Our analysis included studies using unfractionated heparin or LMWH for thromboprophylaxis or treatment in which an outcome variable was new or recurrent VTE and in which the occurrence of HIT was reported. Because our study purpose was to determine the likelihood that VTE, when it does develop, is associated with HIT, we analyzed only studies in which an event occurred. Therefore, our

estimates of VTE frequency do not, nor were intended to, accurately reflect the overall efficacy of heparin therapies. Although HIT-associated thrombosis most typically occurs in the venous circulation, arterial events including myocardial infarction and stroke are also well-documented complications of HIT.^{4–8} Our analysis focused on venous events, and the likelihood that new or recurrent arterial thrombosis in a heparin-treated patient is associated with HIT remains to be investigated.

Using our selection criteria, we identified 10 studies in which a variety of medical and surgical patients received IV or subcutaneous unfractionated heparin or subcutaneous LMWH and were followed up for VTE while in the hospital or at most 90 days. Our analysis did not apply differential weights to the data based on the design of the source study, which included randomized controlled studies as well as prospective and retrospective cohort studies. There was also heterogeneity across other aspects of the studies. For example, although generally similar working definitions for HIT based on platelet count changes were used in the studies, different confir-

Table 3—Frequency of VTE, HIT-Associated VTE, and Their Relative Proportion, by Type of Heparin and Overall*

Study (Year)	Received Heparin, No.	Any VTE	HIT-Associated VTE	HIT-Associated VTE/Any VTE
Unfractionated heparin IV				
Gallus et al ¹³ (1987)	232	15 (6.5)	3 (1.3)	20.0 (4.3–48.1)
Kappers-Klunne et al ¹⁵ (1997)	358†	1 (0.3)	1 (0.3)	100 (2.5–100)
Lindhoff-Last et al ¹⁰ (2002)	375	19 (5.1)	1 (0.3)	5.3 (0.1–26.0)
Buller et al ²⁰ (2003)	1,110	56 (5.0)	0 (0)	0 (0–6.4)
Schmugge et al ¹⁶ (2002)	612‡	38 (6.2)‡	12 (2.0)	31.5 (17.5–48.7)
Overall	2,687	129 (4.8)	17 (0.6)	13.2 (7.9–20.3)
Unfractionated heparin sc				
Girolami et al ¹⁴ (2003)	598	18 (3.0)	1 (0.2)	5.6 (0.1–27.3)
Leyvraz et al ⁹ (1991)	175†	32 (18.3)	2 (1.1)	6.3 (0.8–20.8)
Warkentin et al ¹² (2003)	332	63 (19.0)§	11 (3.3)	17.5 (9.1–29.1)
Overall	1,105	113 (10.2)	14 (1.3)	12.4 (6.9–19.9)
All unfractionated heparin	3,792	242 (6.4)	31 (0.8)	12.8 (8.9–17.7)
LMWH sc				
Buller et al ¹⁹ (2004)	1,107	45 (4.1)	0 (0)	0 (0–7.9)
Leyvraz et al ⁹ (1991)	174†	23 (13.2)	0 (0)	0 (0–14.8)
Lindhoff-Last et al ¹⁰ (2002): lower dose and duration	388	6 (1.5)	0 (0)	0 (0–45.9)
Lindhoff-Last et al ¹⁰ (2002): greater dose and duration	374	11 (2.9)	0 (0)	0 (0–28.5)
Macdonald et al ¹¹ (2003)	51	2 (3.9)	0 (0)	0 (0–84.2)
Warkentin et al ¹² (2003)	333	57 (17.1)§	1 (0.3)	1.8 (0.04–9.4)
Overall LMWH	2,427	144 (5.9)	1 (0.04)	0.7 (0.02–3.8)

*Data are presented as No. (%) or % (95% confidence interval) unless otherwise indicated.

†Patients evaluable for efficacy.

‡Of 612 patients who received heparin for at least 5 d, 57 patients acquired arterial and/or venous thrombosis at a median of 10 d after heparin initiation. Of those 57 patients, plasma was available for antiplatelet antibody testing in 38 patients, and this number of patients (n = 38) is used in frequency estimations.

§Patients with any VTE from Levine et al.¹⁸

||In two patients, confirmatory laboratory testing was not performed, and HIT was diagnosed on the basis of the platelet count criteria being met, other causes of thrombocytopenia being excluded, and the platelet count recovering when heparin therapy was stopped.

matory tests were used that are known to vary in their sensitivity and specificity for HIT.⁴ Although patients remain at increased risk of thrombosis for at least a month after the onset of HIT^{5–8} and have detectable heparin-dependent antibodies for ≥ 4 months,²⁴ only five studies had follow-up beyond hospitalization. HIT-associated thrombotic events may therefore have been underestimated. Despite these limitations, together the studies described 386 heparin-treated patients with VTE (32 patients also with HIT).

Our findings indicate that VTE is infrequently (< 1%) associated with HIT in patients treated with LMWH. However in unfractionated heparin-treated patients, approximately one of eight cases of VTE is associated with HIT. The likelihood that VTE is associated with HIT is significantly greater with unfractionated heparin than LMWH (odds ratio, 21; $p < 0.001$). The prevalence of HIT is generally greater in surgical patients than medical patients,^{4,23} and we also demonstrated a preponderance of surgical patients among heparin-treated individuals with VTE and HIT. Physicians should therefore have a high degree of suspicion for HIT-associated thrombosis in patients, particularly surgical patients, ac-

quiring VTE during or soon after unfractionated heparin therapy, yet lower suspicion with LMWH therapy.

In a patient presenting with VTE, careful history taking concerning any recent hospitalization, heparin exposure, heparin allergy, or platelet problem is important for risk assessment of HIT before initiating anticoagulant therapy.³ Because of the ubiquitous use of heparins, a high percentage of recently hospitalized patients have had heparin exposure. A recent single-center study²⁵ found that 42% of inpatients received unfractionated heparin therapy; exposure to LMWHs and other heparin sources such as heparin-coated devices was not evaluated. Review of previous platelet counts, if available, is prudent, and determination of the current platelet count is essential. Because tests for heparin-platelet factor 4 antibodies typically take several hours to perform, initiation of appropriate anticoagulant therapy usually cannot wait pending their results. In a patient with VTE and strongly suspected HIT, heparins should be avoided and alternative parenteral anticoagulation (argatroban or lepirudin) should be initiated.⁴ Warfarin should not be used as sole therapy because it can worsen the thrombosis and cause

venous gangrene. Its initiation, if desired for longer-term anticoagulation, should be delayed until adequate alternative anticoagulation is provided and the platelet count is at least 100 to $150 \times 10^9/L$.

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